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RESEARCH INVENTION JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES 5(2):101-104, 2025

©RIJSES Publications

ONLINE ISSN: 1115-618X

PRINT ISSN: 1597-2917

https://doi.org/10.59298/RIJSES/2025/52101104

The Role of Gut Microbiota-Derived Metabolites in Modulating Pancreatic β-Cell Senescence: Implications for Type 2 Diabetes Progression

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance and β-cell dysfunction, with emerging evidence highlighting the role of gut microbiota-derived metabolites in modulating pancreatic β-cell senescence. Gut microbiota generates bioactive compounds, including short-chain fatty acids (SCFAs), bile acid derivatives, and amino acid metabolites, which influence β-cell fate through metabolic, inflammatory, and epigenetic pathways. SCFAs, particularly butyrate, exhibit protective effects by enhancing insulin secretion, reducing oxidative stress, and modulating inflammatory responses. Bile acids, through interactions with nuclear receptors such as FXR and TGR5, regulate glucose metabolism and β-cell function. Conversely, dysbiosis-driven shifts in microbial metabolites, including an excess of branched-chain amino acids (BCAAs) and endotoxins like lipopolysaccharides (LPS), exacerbate β-cell senescence via chronic inflammation and mitochondrial dysfunction. This review employed a narrative synthesis methodology, analyzing current literature on microbiota-derived metabolites and their role in β-cell aging. Understanding these interactions provides critical insights into microbiome-based therapeutic strategies for preserving β-cell function and mitigating T2DM progression. Targeted interventions, including probiotics, prebiotics, and dietary modifications, hold promises for modulating gut microbiota composition to enhance metabolic health. Future research should further elucidate microbial metabolite pathways to inform innovative therapeutic approaches aimed at delaying β-cell senescence and T2DM progression.

Keywords: Gut Microbiota-Derived Metabolites, Pancreatic β-Cell Senescence, Type 2 Diabetes Mellitus (T2DM), Short-Chain Fatty Acids (SCFAs), Microbiome-Based Therapeutics.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterized by chronic hyperglycemia due to insulin resistance and progressive pancreatic β-cell dysfunction[1, 2]. While various genetic, environmental, and lifestyle factors contribute to its pathogenesis, emerging evidence suggests that gut microbiota and their metabolites play a pivotal role in metabolic regulation and β-cell homeostasis. The gut microbiome, a diverse community of microorganisms residing in the gastrointestinal tract, produces a variety of bioactive metabolites that can influence host physiology, including immune modulation, inflammation, and energy metabolism [3, 4]. These metabolites, such as short-chain fatty acids (SCFAs), bile acid derivatives, and microbial-derived amino acid metabolites, have been implicated in either protecting against or exacerbating β-cell senescence.

Cellular senescence, a state of permanent growth arrest induced by stressors such as oxidative damage and chronic inflammation, has been increasingly recognized as a key factor in β-cell deterioration [5, 6]. Senescent β-cells exhibit impaired insulin secretion, altered metabolic activity, and enhanced pro-inflammatory signaling, contributing to the progressive decline in functional β-cell mass observed in T2DM. Notably, gut microbiota-derived metabolites have emerged as critical modulators of β-cell fate, influencing senescence pathways through epigenetic modifications,

inflammatory cascades, and mitochondrial function. Understanding the intricate relationship between gut microbiota-derived metabolites and β-cell senescence holds promise for novel therapeutic strategies aimed at preserving β-cell function and mitigating T2DM progression. This review explores the current knowledge on microbiota-derived metabolites and their mechanistic roles in modulating β-cell senescence, highlighting potential translational opportunities for microbiome-based interventions in T2DM management.

Gut Microbiota Composition and Metabolite Production in Health and Disease

The gut microbiota consists of trillions of microorganisms, primarily bacteria, which establish a symbiotic relationship with the host [7, 8]. In healthy individuals, microbiota maintains homeostasis by producing key metabolites that regulate metabolic and immune functions. However, dysbiosis an imbalance in microbial composition is commonly observed in individuals with T2DM, characterized by reduced microbial diversity and altered metabolite profiles. Several bacterial genera, such as Firmicutes and Bacteroidetes, play essential roles in producing metabolites that impact β-cell function.

SCFAs, including acetate, propionate, and butyrate, are fermented by products of dietary fiber by commensal bacteria [9]. These metabolites have been shown to exert beneficial effects on β-cells by enhancing glucose-stimulated insulin secretion, reducing oxidative stress, and modulating inflammatory responses. Conversely, an overabundance of branched-chain amino acids (BCAAs) and lipopolysaccharides (LPS), often linked to an altered gut microbiota, has been associated with metabolic inflammation and impaired β-cell function. These findings underscore the importance of gut microbiota-derived metabolites in regulating β-cell health and disease.

Short-Chain Fatty Acids and β-Cell Senescence

SCFAs, particularly butyrate, have garnered attention for their protective effects against cellular senescence. Butyrate acts as a histone deacetylase (HDAC) inhibitor, promoting chromatin remodeling and enhancing the expression of genes involved in β-cell survival and function [10]. Additionally, SCFAs activate G-protein-coupled receptors (GPCRs), such as FFAR2 and FFAR3, leading to improved insulin secretion and reduced inflammatory cytokine production. Experimental studies indicate that butyrate supplementation alleviates endoplasmic reticulum (ER) stress, a known trigger of β-cell senescence [11]. Furthermore, SCFAs enhance mitochondrial function by promoting oxidative phosphorylation and reducing reactive oxygen species (ROS) production, key contributors to cellular aging. These mechanisms collectively suggest that SCFA-producing bacteria play a crucial role in maintaining β-cell integrity, and dietary interventions aimed at increasing SCFA production may represent a viable strategy for delaying β-cell senescence in T2DM.

Bile Acid Metabolism and β-Cell Function

Bile acids, traditionally recognized for their role in lipid digestion, also function as signaling molecules influencing glucose homeostasis [12]. Gut microbiota modulates bile acid composition through deconjugation and biotransformation, leading to the generation of secondary bile acids that interact with nuclear receptors, such as the farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5).

Activation of FXR and TGR5 has been shown to enhance insulin sensitivity and β-cell function [13]. TGR5 stimulation by microbiota-modified bile acids promotes glucagon-like peptide-1 (GLP-1) secretion, which in turn improves insulin release and reduces β-cell stress. However, excessive bile acid accumulation may exert cytotoxic effects on β-cells, highlighting the need for balanced bile acid metabolism to prevent β-cell dysfunction.

Microbial-Derived Amino Acid Metabolites and β-Cell Aging

Amino acid metabolism by gut bacteria produces bioactive metabolites that influence cellular senescence [13, 14]. Tryptophan metabolites, such as indole derivatives, can modulate inflammatory pathways through activation of the aryl hydrocarbon receptor (AhR), which has been implicated in metabolic homeostasis and β-cell survival.

On the other hand, increased levels of BCAAs, particularly leucine, isoleucine, and valine, have been associated with insulin resistance and β-cell dysfunction. Elevated BCAA levels correlate with increased mTOR signaling, a pathway that drives cellular aging and impairs insulin secretion. These findings suggest that targeting gut microbiota-mediated amino acid metabolism may provide a novel approach to mitigating β-cell senescence and preserving pancreatic function in T2DM.

Inflammatory Mediators and the Gut-β-Cell Axis

Chronic low-grade inflammation is a hallmark of T2DM and plays a crucial role in β-cell senescence [15]. Gut microbiota-derived endotoxins, such as LPS, trigger inflammatory pathways through toll-like receptor 4 (TLR4) activation, leading to increased cytokine production and oxidative stress [16]. β-cells, which are highly sensitive to inflammatory insults, undergo senescence when exposed to prolonged inflammatory stimuli, resulting in reduced insulin secretion and impaired glucose homeostasis. Probiotic and prebiotic interventions have demonstrated

potential in modulating gut microbiota composition and reducing inflammatory burden [17]. Certain Lactobacillus and Bifidobacterium strains exhibit anti-inflammatory properties by inhibiting NF-κB signaling and promoting the production of anti-inflammatory cytokines such as IL-10. Thus, microbiota-targeted therapies aimed at reducing inflammation may offer promising avenues for preserving β-cell function and delaying T2DM progression.

CONCLUSION

The gut microbiota and its metabolites play a fundamental role in modulating pancreatic β-cell senescence, influencing T2DM progression through a complex interplay of metabolic, inflammatory, and epigenetic mechanisms. SCFAs, bile acid derivatives, and microbial-derived amino acid metabolites exhibit both protective and detrimental effects on β-cell aging, highlighting the importance of microbial balance in maintaining pancreatic function. Dysbiosis-driven shifts in metabolite profiles contribute to chronic inflammation, oxidative stress, and impaired insulin secretion, accelerating β-cell senescence and disease progression.

Targeting gut microbiota through dietary modifications, probiotics, and microbiome-based therapies holds significant promise for mitigating β-cell deterioration in T2DM. Future research should focus on elucidating the precise mechanisms underlying microbial metabolite interactions with β-cell pathways, paving the way for novel therapeutic interventions that harness gut microbiota-derived metabolites to improve metabolic health. Addressing the gut-β-cell axis represents a crucial frontier in diabetes management, offering potential strategies to preserve β-cell function and delay T2DM onset and progression.

REFERENCES

1. Alum, E. U., Ugwu, O.P.C., Obeagu, E.I., Aja, P.M.: Nutritional Care in Diabetes Mellitus: A Comprehensive Guide. International Journal of Innovative and Applied Research. 2023; 11(12):16-25. https://doi.org/10.58538/IJIAR/2057
2. Ugwu, O.P.C., Kungu, E., Inyangat, R., Obeagu, E. I., Alum, E. U., Okon, M. B., Subbarayan, S. and Sankarapandiyan, V.: Exploring Indigenous Medicinal Plants for Managing Diabetes Mellitus in Uganda: Ethnobotanical Insights, Pharmacotherapeutic Strategies, and National Development Alignment. INOSR Experimental Sciences. 12, 214–224 (2023). https://doi.org/10.59298/INOSRES/2023/2.17.1000
3. Santhiravel, S., Bekhit, A.E.D.A., Mendis, E., Jacobs, J.L., Dunshea, F.R., Rajapakse, N., Ponnampalam, E.N.: The Impact of Plant Phytochemicals on the Gut Microbiota of Humans for a Balanced Life. International Journal of Molecular Sciences 2022, Vol. 23, Page 8124. 23, 8124 (2022). https://doi.org/10.3390/IJMS23158124
4. Liu, J., Tan, Y., Cheng, H., Zhang, D., Feng, W., Peng, C.: Functions of Gut Microbiota Metabolites, Current Status and Future Perspectives. Aging Dis. 13, 1106 (2022). https://doi.org/10.14336/AD.2022.0104
5. Li, N., Liu, F., Yang, P., Xiong, F., Yu, Q., Li, J., Zhou, Z., Zhang, S., Wang, C.Y.: Aging and stress induced β cell senescence and its implication in diabetes development. Aging (Albany NY). 11, 9947 (2019). https://doi.org/10.18632/AGING.102432
6. Lee, H., Sahin, G.S., Chen, C.W., Sonthalia, S., Cañas, S.M., Oktay, H.Z., Duckworth, A.T., Brawerman, G., Thompson, P.J., Hatzoglou, M., Eizirik, D.L., Engin, F.: Stress-induced β cell early senescence confers protection against type 1 diabetes. Cell Metab. 35, 2200-2215.e9 (2023). https://doi.org/10.1016/J.CMET.2023.10.014/ATTACHMENT/6F1AE52E-DF2E-46E9-9762-EA6363F029D6/MMC5.XLSX
7. Ugwu, O. P. C., Alum, E. U., Okon, M. B., Obeagu, E. I. Mechanisms of microbiota modulation: Implications for health, disease, and therapeutic interventions. Medicine (Baltimore). 2024 May 10;103(19):e38088. doi: 10.1097/MD.0000000000038088.
8. Gomaa, E.Z.: Human gut microbiota/microbiome in health and diseases: a review. Antonie van Leeuwenhoek 2020 113:12. 113, 2019–2040 (2020). https://doi.org/10.1007/S10482-020-01474-7
9. Vinelli, V., Biscotti, P., Martini, D., Del Bo', C., Marino, M., Meroño, T., Nikoloudaki, O., Calabrese, F.M., Turroni, S., Taverniti, V., Caballero, A.U., Andrés-Lacueva, C., Porrini, M., Gobbetti, M., De Angelis, M., Brigidi, P., Pinart, M., Nimptsch, K., Guglielmetti, S., Riso, P.: Effects of Dietary Fibers on Short-Chain Fatty Acids and Gut Microbiota Composition in Healthy Adults: A Systematic Review. Nutrients. 14, 2559 (2022). https://doi.org/10.3390/NU14132559/S1
10. Cho, J.H., Chae, C.W., Lim, J.R., Jung, Y.H., Han, S.J., Yoon, J.H., Park, J.Y., Han, H.J.: Sodium butyrate ameliorates high glucose-suppressed neuronal mitophagy by restoring PRKN expression via inhibiting the RELA-HDAC8 complex. Autophagy. 20, 1505–1522 (2024). https://doi.org/10.1080/15548627.2024.2323785

11. Weldemariam, M.M., Woo, J., Zhang, Q.: Pancreatic INS-1 β-Cell Response to Thapsigargin and Rotenone: A Comparative Proteomics Analysis Uncovers Key Pathways of β-Cell Dysfunction. Chem Res Toxicol. 35, 1080–1094 (2022). https://doi.org/10.1021/ACS.CHEMRESTOX.2C00058/SUPPL_FILE/TX2C00058_SI_002.XLSX
12. Wang, Y., Xu, H., Zhou, X., Chen, W., Zhou, H.: Dysregulated bile acid homeostasis: unveiling its role in metabolic diseases. Medical Review. 4, 262–283 (2024). https://doi.org/10.1515/MR-2024-0020/ASSET/GRAPHIC/J_MR-2024-0020_FIG_007.JPG
13. Wang, Y., Yu, J., Chen, B., Jin, W., Wang, M., Chen, X., Jian, M., Sun, L., Piao, C.: Bile acids as a key target: traditional Chinese medicine for precision management of insulin resistance in type 2 diabetes mellitus through the gut microbiota-bile acids axis. Front Endocrinol (Lausanne). 15, 1481270 (2024). https://doi.org/10.3389/FENDO.2024.1481270/PDF
14. Hosseinkhani, F., Heinken, A., Thiele, I., Lindenburg, P.W., Harms, A.C., Hankemeier, T.: The contribution of gut bacterial metabolites in the human immune signaling pathway of non-communicable diseases. Gut Microbes. 13, 1–22 (2021). https://doi.org/10.1080/19490976.2021.1882927
15. Kruczkowska, W., Gałęziewska, J., Kciuk, M., Gielecińska, A., Płuciennik, E., Pasieka, Z., Zhao, L.Y., Yu, Y.J., Kołat, D., Kałuzińska-Kołat, Ż.: Senescent adipocytes and type 2 diabetes – current knowledge and perspective concepts. Biomol Concepts. 15, (2024). https://doi.org/10.1515/BMC-2022-0046/ASSET/GRAPHIC/J_BMC-2022-0046_FIG_001.JPG
16. Candelli, M., Franza, L., Pignataro, G., Ojetti, V., Covino, M., Piccioni, A., Gasbarrini, A., Franceschi, F.: Interaction between Lipopolysaccharide and Gut Microbiota in Inflammatory Bowel Diseases. International Journal of Molecular Sciences 2021, Vol. 22, Page 6242. 22, 6242 (2021). https://doi.org/10.3390/IJMS22126242
17. Bilal, M., Ashraf, S., Zhao, X.: Dietary Component-Induced Inflammation and Its Amelioration by Prebiotics, Probiotics, and Synbiotics. Front Nutr. 9, 931458 (2022). https://doi.org/10.3389/FNUT.2022.931458/PDF

CITE AS: Kibibi Muthoni L. (2025). The Role of Gut Microbiota-Derived Metabolites in Modulating Pancreatic β-Cell Senescence: Implications for Type 2 Diabetes Progression. RESEARCH INVENTION JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES 5(2):101-104. https://doi.org/10.59298/RIJSES/2025/52101104